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Intoxication Digitalique

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Abstract

Despite being very familiar with digitalis, its use always asks for particular attention. Therapeutic index is narrow increasing the risk of intoxication. Digitalis intoxication shows itself in electrocardiogram (ECG) abnormalities that can lead to arrhythmia potentially fatal and in different signs and symptoms that are not specific. The treatment is based on the patient risk level. Treatment associated to low- risk situations will include temporary suspension of the therapy, ECG, follow-up and electrolytic supplements if necessary. The administration of agents such as phenytoin, lidocaine, atropine and/or the installation of a pacemaker can proved to be necessary in the presence of significant dysrythmia. Finally, the administration of DigiFab® (antibody fragments specific for digoxin) is indicated in cases where other advance or used treatments proved to be inappropriate and for the treatment of arrhythmia potentially fatal. However, since the cost of a DigiFab® treatment is very expensive, its use must be justified.

Keywords: Arhythmia; Digoxin; Digitalis; Intoxication; Immunotherapy

Introduction

The digitalis glycosides are known for long to the medical world. Discovered by William withering, physician and botanist of the XVIII century. The digitalis glycosides constitute a homogeneous group of cardiotonics glycosides with different pharmacokinetic properties, digoxin is the digitalis currently used. It is part of the arsenal therapeutic of atrial fibrillation, supraventricular tachycardia and congestive heart failure. Despite our great familiarity with this molecule, its use requires a special attention since it has a narrow therapeutic index [1]. We also recall, that there is a large inter-individual variability in the response to the effect of digoxin.

Physiological recall

"The calcium release by inducing calcium" is at the origin of the contraction of the cardiomyocyte. At the level of the cardiomyocyte, Ca2+ extracellular penetrate each depolarization via calcium voltage channels associated to type L. The slightly moderate increase , in the intracellular calcium concentration induces the release of Ca2+ stored in the cytoplasmic endoplasmic reticulum, via the ryanodine receptor RYR, it's what we refer to as " the release of Ca2 induced by Ca2" (Figure 1). The increase in the intracellular calcium is essential to interaction with the contractile proteins, as well as allowing muscular contraction [2,3].

During the cardiomyocytes repolarization, the intracellular Ca2 is again sequestered in the sarcoplasmic reticulum by a Ca2+ ATPase and by a Na+/Ca2+. The ability of an exchange of this Na+/Ca2+ is strongly connected to the intracellular concentration of sodium. In fact, on one hand the antiporter uses the sodium gradient to move calcium to the extracellular space against

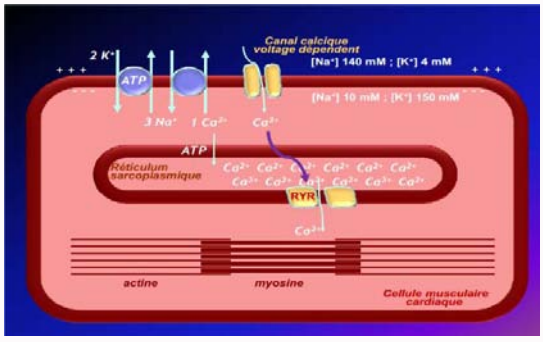

Figure 1: Mechanism of contraction of cardiomyocytes.

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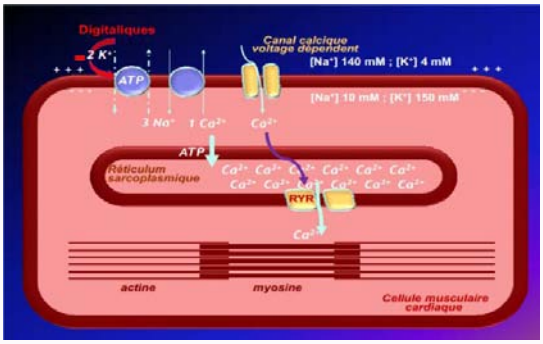

Figure 2: Mechanism of myocardial action of digitalis.

his own concentration gradient. On the other hand, the extracellular concentrations of Na+/Ca2+, are much less variable than the intracellular concentrations in physiological conditions. The incoming sodium to the cell is then outsourced by the Na+/K+ ATPase. In fact, by extracting the intracellular sodium, the Na+/K+ ATPase pomp is the main determinant of the intracellular concentration of sodium. The next sodic influx.

Mechanism of Action

Positive inotropic effect

The digitalis glycosides are powerful and very selective inhibitors of the active transmembrane transportation of Na+ and K+. The liaison of the digitalis glycosides to the Na+/K+ ATPase pump leads to an elevation of the intracellular sodic concentrations. Which decreases the sodic transmembrane gradient responsible for moving out calcium by the antiporter, while calcium continues to enter to the cell in each depolarization. Therefore, more calcium is stocked in the sarcoplasmic reticulum, where more calcium is available to the next cellular depolarization and increase in the myocardial contraction (Figure 2).

Electrophysiological action

At therapeutic concentrations, the digitalis glycosides decrease automaticity and slow atrioventricular conduction. These phenomena are related to an increase in the vagal tone and a decrease in the adrenergic one. At higher concentrations, they increase the ventricular excitability.

Effect of the sympathetic tone regulation

There is a direct effect of digitalis glycosides on the carotid baroreflex response to pressure variations (diminished sensitivity in heart failure, might be restored by inhibition of the baroreceptors ATPase), inducing a decrease in the sympathetic tone. This decrease in neuro-hormonal activation represents a significant part in the action of digitalis glycosides [2,3].

Pharmacokinetic Characteristics and Precautions of Use

The digoxin is administrated in a single daily take. It is mainly present under free form in the blood, not bounded to plasma proteins in 80%, which justify its rapidity of action: beginning of action 10 to 30 minutes by injection, 1 to 2 hours orally. The main tissular reservoir is the skeletal muscle; with a large volume of distribution (5 L/kg) this explains the poor efficiency of dialysis in this case (Table 1).

The margin between the therapeutic dose and the toxic one is very narrow, which requires the need for a regular monitoring especially a clinical one, particularly in case of elderly, renal failure and the risk of drugs associations (Table 2).The recommended therapeutical concentrations are of 0.9 to 2ng/ml. Recent studies set this margin to 0.5 -0.8 ng/ml in the treatment of congestive heart failure. The toxicity is usually manifested in rates higher than 2 ng/ml.

Digitalis Intoxication

The digitalis intoxication may occur as a result of a drug interaction (Table 2), a use of supra-therapeutical doses or a decrease in renal elimination. Furthermore, despite therapeutical serum doses, an intoxication to the digoxin may appear in cases where the myocardial sensitivity is increased such as in hypothyroidism, advanced age, advanced heart diseases, myocardial ischemia, hypoxemia, electrolytic disorders and Acido-basic [1-4].

Clinical manifestations

Digestive disorders, neurosensorial disorders and cardiovascular disorders are classically associated in clinical table of the digitalis intoxication. The first may make appeal to a diagnosis in the case of a patient treated by digitalis. The last two are responsible for this intoxication.

The clinical presentation of acute intoxication differs a little from that of a chronic intoxication.

Digestive disorders

Vomiting is the result of an excitatory action of digitalis glycosides on the postrema area. They are frequent and at very early stage without. Their presence, in the case of a chronic digitalis treatment can cause an overdose. Other digestive disorders, abdominal pain such as cramps and diarrhea are sometimes observed reflecting vagal hyperactivity.

Neurosensorial disorders

Approximately one quarter of the patients suffer in early stages from clouding of consciousness, somnolence or restlessness with anguish. Headache, myalgia, asthenia are also frequent. In addition, Ocular disorders, dyschromatopsias with colorful aureoles, glittering scotomas, blurred and/or scrapie vision, or rarely micropsia and

Table 1: Pharmacokinetic characteristics.

	Half life	Absorption	Metabolism	Elimination
Digoxine	36H	70%	Free form Large volume of distribution (5l/kg)	Negligible liver biotransformation

Table 2: Drug Interactions of Digitalis.

Drug interaction	Mechanism and consequence of interaction
All hypokalemic drugs (diuretics, laxatives, corticosteroids, amphotericin B)	Increased toxicity of digitalis
Calcium by injection	Increased toxicity of digitalis
Phenobarbital phenytoin	Decreased plasma concentrations

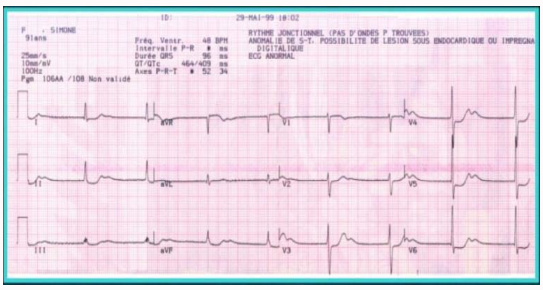

Figure 3: Sino-atrial block 3rd-degree with junctional exhaust at 40cpm, flattening of the T-waves and digital cup of the ST segment.

Table 3: Calculation of the number of digiFab® vials to be administered.

Acute intoxication	Chronic intoxication
Number of vials = Mg digoxin ingested x 0.8*/ 0.5** If undetermined quantity give 20 vials.	Number of vials = Digoxinemia (mmol / l) x 0.781 x wt (kg)/100 If unknown serum level give 6 vials.

* Bioavailability; **Amount of digoxin bound per vial.

amblyopia are possible side effects.

Cardiac manifestations

Responsible for all the prognosis of digitalis intoxication, whatever it might be acute or chronic.

Conduction disturbances

Can be very early stage with a risk of evolution of severe bradycardia or even an asystole. All type of conduction disturbances may occur, requiring an urgent treatment (Figure 3).

Automatism disturbances

To the ventricular floor it may consist of a ventricular extra systoles, more or less frequent, and tachycardia or ventricular fibrillation. The latter have a pejorative prognostic value. It is recalled that the signs of glycosides digitalis impregnations may manifest at therapeutical doses. These electrical changes happen to the T wave and the ST segment with a flattening of the T wave, which becomes negative but remains asymmetric, lowering of the J-point and a sub-offset of the ST segment characterized by a cupule to the upper concavity called "cupule digitalis" (Figure 3).

Therapeutical Care

Once the diagnosis of intoxication digitalis is established, the treatment to use will depend on the degree of risk associated to the patient:

- The case is characterized low risk in the absence of change in the electrocardiogram (ECG), the slightest increase in the digoxinemia (normal 1.0 to 2.6 nmol/L), the absence of a history of severe heart diseases and a fraction of normal ejection (>50%). The treatment is a temporary inhibition of digoxin under electrical supervision, a control of digoxinemia, monitoring and use of electrolytic supplements when needed.

- The case is characterized intermediate risk when there are changes in the ECG without potentially lethal complications. The treatment consists of electrolytic controls, supplements when needed and anti-arrhythmic agents if there is a significant presence of dysrhythmias.

- The case is characterized high risk when there exist potentially fatal arrhythmias and extremely high digoxinémies (Table 4). For an ingestion of a high dose the treatment is a gastric lavage (If ≤1-2 h post ingestion), in addition to, the administration of activated charcoal (If ≤6-8 h post ingestion) [4].

Atropine administration must be taken into account in case of sinus bradycardia or atrioventricular block (AV) of the second and third degree to correct the effects of vagal stimulation. The repetition of doses is often necessary. A Hemodynamically unstable state and a resistance to atropine may require the installation of a pacemaker endo-venous. However, the insertion of the probe in the Ventricle risks inducing a ventricular arrhythmia and therefore it is suggested to administrate lidocaine first [5]. In fact, the intravenous lidocaine (IV) or phenytoin by either oral or intravenous controls effectively arrhythmias induced by the digitalis intoxication. The digoxin has a large volume of distribution (5.6 L/kg) and a strong tissular liaison. Therefore, any process of dialysis would be effectively of limit. Finally, the anti digitalic antibodies can reverse the effect of digoxin in neutralizing its free fraction in serum and extracellular [5].

This decrease in the free fraction in plasma promotes the dissociation of digoxin at the level of its binding sites. Thus, the heart rate standardizes usually on a period of 30 minutes to 4 hours (average delay of 90 minutes) following the administration of the fragments of specific digoxin antibodies. The duration of the antibody complex- digoxin serum's half-life is approximately 16 to 20 hours. The latter may double in case of a renal failure. Thus, the digoxinemia may only be interpreted adequately few days after its administration. Patients with severe renal impairment should be the subject of a prolonged follow up because it is not known with certainty if the inability to eliminate the antibody complex-digoxin may translate into a liberation of digoxin [6].

Use of Antidigitalic Anticoprs Digifab®

The antidigitalic antibodies are currently marketed under the commercial denomination DigiFab®; the Digidot® and Digibind® are no longer in use. The efficacy and safety of the early immunological treatment by Fab antibodies has modified the therapeutical approach and prognostic [7]. However, it remains under-used [8]. The high cost often limits the access to the hospital centers [7].

The efficiency, safety, specificity and the positive ratio of benefits/costs of the administration of DigiFab® have been demonstrated [9]. Adding, that the DigiFab® is the only effective treatment against the hyperkaliemia associated with the digitalis intoxication.

Table 4: Indications for DigiFab® Antidigital Antibodies.

Equimolar Neutralization	Semi-molar neutralization
In the presence of a single pejorative factor:	In the presence of at least three pejorative factors:
- Ventricular arrhythmia - Severe Bradycardia <40cpm resistant to atropine - Kalemia >5.5mmol / l - Cardiogenic shock - Mesenteric infarction	- Males - Pre-existing heart disease - Age >55 years - BAV whatever the degree - Bradycardia <50cpm and resistant to atropine - Kalemia> 4.5mmol/l.

Posology

Start by a test dose to eliminate any allergic reaction to the Fab fragment, particularly if there has been already administration of Fab fragments [1,5,6]. Allergic reactions associated with the DigiFab® are less than 1%. The dose depends on the quantity of digoxin present in the body. The calculation will be based either on the amount ingested in case of an acute intoxication, or on the digoxin serum's concentration at equilibrium level of in situations of chronic intoxication (Table 3).

Administration

DigiFab® is administered by injection over a period of 30 minutes. The solution should be previously filtered with a 0.22 micron filter, in order to avoid the administration of dissolved particles. We can resort to injection IV bolus dose if the cardiac arrest becomes imminent. After the administration, it is recommended to monitor the potassium regularly during few hours due to the risk of hypokalemia following the reactivation of the Na+/K+ ATPase pump. We must as well monitor the symptoms. The resurgence of symptoms of congestive heart failure and an immediate ventricular response in an Atrial Fibrillation (AF) context appears after the loss of the digoxin effect [10]. A second Antidote dose is founded at the onset of clinical signs associated with a pejorative factor (Table 4).

Conclusion

Digitalis intoxication is a frequently encountered case in current practice. The cardiac complications often engage the vital prognosis imposing adequate support and quick response. DigiFab® occupies a key place in the support of high-risk patients. By contrast, since the cost of DigiFab® treatment is high, its use must be justified.

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